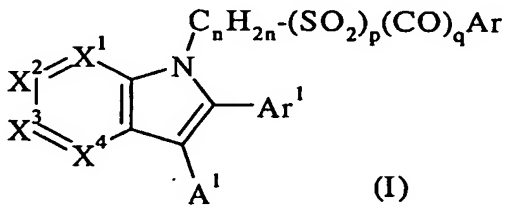
Indoles and azaindoles as antiviral agents

The present invention relates to indole and azaindole compounds, to pharmaceutical compositions containing them, to their use in the prevention and treatment of hepatitis C infections and to methods of preparation of such compounds and compositions.

Hepatitis C (HCV) is a cause of viral infections. There is as yet no adequate treatment for HCV infection but it is believed that inhibition of its RNA polymerase in mammals, particularly humans, would be of benefit. International patent applications WO 01/47883, WO 02/04425 and WO 03/000254 suggest fused ring compounds as possible inhibitors of HCV polymerase and illustrate thousands of possible benzimidazole derivatives that possess HCV polymerase inhibitory properties. However, these patent applications do not describe or reasonably suggest the preparation of any benzimidazole or azabenzimidazole substituted on all three available sites on the fused imidazole ring. WO 03/010140 and WO 03/010141 suggest further fused ring compounds as possible inhibitors of HCV polymerase and illustrate thousands of possible compounds all of which possess complex esterified side chains. None of these patent applications describe an indole or azaindole in which the indole nitrogen is substituted by an aromatic residue as described in the present application.

The present invention provides compounds of the formula (I):



(I)

wherein:

Ar is a moiety containing at least one aromatic ring and possesses 5-, 6-, 9- or 10-ring atoms 0 to 3 of which may be N, O or S heteroatoms of which at most 1 will be O or S; which moiety may be optionally substituted by groups Q^1, Q^2 or Q^3 wherein Q^1 is a hydroxy group, fluorine, chlorine, bromine or iodine atom or a C_{1-6}alkyl, C_{1-6}alkyl substituted by not more than 5 fluorine atoms, C_{1-6}alkoxyl,

C_{1-6}alkoxyl substituted by not more than 5 fluorine atoms, C_{2-6}alkenyl, C_{2-6}alkynyl, $(CH_2)_{0-3}N(C_{1-4}alkyl)_2$, nitro, cyano, nitrile, carboxyl, esterified carboxy wherein the esterifying moiety has up to 4 carbon atoms optionally substituted by not more than 5 fluorine atoms; or $-SO_2(C_{1-6}alkyl)$,

Q_2 is a fluorine, chlorine, bromine or iodine atom or a methyl, trifluoromethyl, methoxy, trifluoromethoxy or difluoromethoxy group,

Q_3 is a fluorine, chlorine, bromine or iodine atom or a methyl, methoxy, trifluoromethoxy or difluoromethoxy group;

Ar^1 is a moiety containing at least one aromatic ring and possesses 5-, 6-, 9- or 10-ring atoms 0 to 3 of which may be N, O or S heteroatoms of which at most 1 will be O or S; which moiety may be optionally substituted by groups Q^4, Q^5 or Q^6 wherein Q^4 is a hydroxy group, fluorine, chlorine, bromine or iodine atom or a C_{1-6}alkyl, C_{1-6}alkyl substituted by not more than 5 fluorine atoms, C_{1-6}alkoxyl, C_{1-6}alkoxyl substituted by not more than 5 fluorine atoms, C_{2-6}alkenyl, C_{2-6}alkynyl, $(CH_2)_{0-3}N(C_{1-4}alkyl)_2$, nitro, cyano, nitrile, carboxyl, esterified carboxy wherein the esterifying moiety has up to 4 carbon atoms optionally substituted by not more than 5 fluorine atoms,

Q^5 is a fluorine, chlorine, bromine or iodine atom or a methyl, trifluoromethyl, methoxy, trifluoromethoxy or difluoromethoxy group,

Q^6 is a fluorine, chlorine, bromine or iodine atom or a methyl, methoxy, trifluoromethoxy or difluoromethoxy group;

X^1 is N or CR^a; X^2 is N or CR^1; X^3 is N or CR^2; X^4 is N or CR^b; with the proviso that at least one of X^2 and X^3 is not N; wherein R^a and R^b are independently selected from hydrogen, fluorine or chlorine or C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkyl or alkoxy optionally substituted by up to 6 fluorine atoms and/or a hydroxyl group;

n is 0, 1, 2, 3, 4, 5 or 6;

p+q is 0 or 1;

A^1 is C_{1-6}alkyl, C_{2-6}alkenyl, or C_{1-6}alkyl or C_{2-6}alkenyl substituted by C_{1-4}alkoxy or up to 5 fluorine atoms or a non-aromatic ring of 3 to 8 ring atoms which may contain a double bond and which may contain a O, S, SO, SO_2 or NH moiety and which may be optionally substituted by one or two alkyl groups of up to 2 carbon atoms or by 1 to 8 fluorine atoms;

one of R^1 and R^2 is a Het or is hydrogen, fluorine, chlorine or bromine atom or a C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkyl or alkoxy substituted by up to 5 fluorine atoms, nitrile, carboxy, C_{1-4}alkoxycarbonyl, C_{1-4}alkyl or C_{2-4}alkenyl substituted by a carboxy or C_{1-4}alkoxycarbonyl group, or a NR^3R^4, $SO_2NR^3R^4$ or $CONR^3R^4$ group where R^3 is hydrogen, C_{1-4}alkyl, SO_2R^5 or COR^5 and R^4 is hydrogen, hydroxyl or C_{1-4}alkyl or R^3 and R^4 are alkylene linked to form a 5- or 6-membered ring, and R^5 is C_{1-4}alkyl optionally substituted by up to 5 fluorine atoms;

Het is a 5 or 6-membered aromatic ring of which 1, 2, 3 or 4 ring atoms may be selected from N, O, S with at most 1 being O or S which ring may be substituted by 1 or 2 groups selected C_{1-4}alkyl or hydroxy or tautomers thereof, or is 2-hydroxy-cyclobutene-3,4-dione;

the other of R^1 and R^2 is a hydrogen, fluorine or chlorine atom or C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkyl or alkoxy substituted by up to 6 fluorine atoms and optionally a hydroxyl;

or a pharmaceutically acceptable salt thereof.

The group C_nH_{2n} may be straight or branched such as a $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-CH_2-CH(CH_3)-$, $-CH(CH_3)-CH_2-$ or the like straight or branched butyl, pentyl or hexyl group. Most suitably the C_nH_{2n} group is a $-CH_2-$ group.

When used herein C_{1-6}alkyl means methyl, ethyl, 1-propyl, 2-propyl or a straight or branched butyl, pentyl or hexyl group. Particularly apt C_{1-6}alkyl groups are methyl, ethyl, propyl and butyl groups. Favoured alkyl groups are ethyl and methyl groups. The methyl group is the preferred alkyl group.

Most suitably a C_{1-6}alkyl group substituted by up to 5 fluorine atoms will include a CF_3, CHF_2 and/or CF_2 moiety. Favoured fluoroalkyl groups are the CF_3, CH_2F and CF_2CF_3 groups. The CF_3 group is the preferred fluoroalkyl group.

When used herein C_{2-6}alkenyl means a $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=C(CH_3)$, $-C(CH_3)=C(CH_3)$ or straight or branched pentylene or hexylene groups.

When used herein C_{1-6}alkoxy and fluorinated C_{1-6}alkoxy are analogous to the alkyl and fluoroalkyl groups described above so that, for example, preferred groups include OCH_3, OCF_3 and $OCHF_2$ groups.

Favoured values for R^a and R^b independently include hydrogen, fluorine, methyl, methoxy and trifluoromethyl. Particularly apt values for R^a and R^b include hydrogen or fluorine. A preferred value for R^a is hydrogen. A preferred value for R^b is hydrogen.

The Ar moiety may contain a single aromatic ring or one aromatic ring to which a further aromatic or non-aromatic ring is fused.

Favoured values for Ar include optionally substituted 6-membered heteroaromatic groups with 1, 2 or 3 nitrogen ring atoms; unsubstituted or substituted 5-membered heteroaromatic groups with 1, 2, 3 or 4 nitrogen ring atoms; unsubstituted or substituted 5-membered heteroaromatic groups with one nitrogen ring atom and one oxygen or sulfur ring atoms; unsubstituted or substituted 5-membered heteroaromatic groups with two nitrogen atoms and one oxygen or sulfur atom. The optional substituents on such rings include one or two fluorine, chlorine, bromine, C_{1-4}alkyl, hydroxyl, C_{1-4}alkoxy or CF_3 groups of which methyl and hydroxyl are preferred.

Particularly apt values for Ar also include phenyl and substituted phenyl or the formula $C_6H_2Q^1Q^2Q^3$ of which phenyl, fluorophenyl, difluorophenyl, chlorophenyl, bromophenyl, dibromophenyl, methylphenyl, methoxyphenyl, methylsulfonylphenyl, carboxyphenyl, cyanophenyl, trifluoromethylphenyl and the like are preferred.

Ar is aptly an optionally substituted phenyl, pyridyl, imidazolyl, thiazolyl or oxadiazolyl group. The optional substituents on such groups include one or two fluorine, chlorine, bromine, C_{1-6}alkyl, hydroxyl, C_{1-6}alkoxy, CF_3, cyano, carboxyl, methylsulfonyl or $(CH_2)_{0-3}N(C_{1-4}alkyl)_2$ groups, of which methyl, fluoro, chloro, bromo, cyano, carboxyl, methylsulfonyl and $CH_2N(CH_3)_2$ are preferred.

Preferably Ar is a group selected from phenyl, methylphenyl, mono- or difluorophenyl, mono- or dichlorophenyl, mono- or dibromophenyl, cyanophenyl, carboxyphenyl, methylsulfonylphenyl, pyridyl, imidazolyl or methylthiazolyl. More particularly Ar is phenyl, 2-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-methylphenyl, 4-methylphenyl, 3,5-dibromophenyl, 4-methylsulfonylphenyl, 3-carboxyphenyl, pyrid-2-yl, pyrid-3-yl, 2-methyl-1,3-thiazol-4-yl, 1H-imidazol-4-yl or 5-[(dimethylamino)methyl]-1,2,4-oxadiazol-3-yl.

Favourably n is 0, 1 or 2.

In one embodiment p is 1 and q is 0. In another embodiment p is 0 and q is 1. Alternatively p and q are both 0.

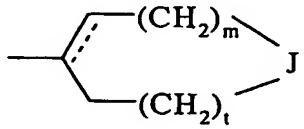
The Ar^1 moiety may contain a single aromatic ring or one aromatic ring to which a further aromatic or non-aromatic ring is fused.

Ar^1 is aptly phenyl, naphthyl, indolyl, tetrahydronaphthyl, pyridyl, imidazolyl, furyl, thienyl, pyrolidyl, oxazolyl, thiazolyl, pyrazolyl, pyridazolyl, triazolyl, oxadiazolyl, thiodiazolyl or quinonyl, any of which may be optionally substituted by group Q^4, Q^5 or Q^6 as hereinbefore defined.

Favourably, Ar^1 is a pyridyl, furyl or thienyl group or a group of the formula $C_6H_2Q^4Q^5Q^6$. One particularly favoured group Ar^1 is the pyridyl group. Other particularly favoured Ar^1 groups are optionally substituted phenyl groups of the formula $C_6H_3Q^1Q^2$ of which phenyl, fluorophenyl, chlorophenyl, hydroxyphenyl, trifluoromethylphenyl, methoxyphenyl, difluorophenyl, dichlorophenyl, {[isopropyl(methyl)amino]-methyl}phenyl and the like are preferred.

Preferably Ar^1 is phenyl, methoxyphenyl, fluorophenyl, chlorophenyl, hydroxyphenyl, pyridyl or {[isopropyl(methyl)amino]-methyl}. More particularly Ar^1 is phenyl, 4-methoxyphenyl, 2-fluorophenyl, 4-hydroxyphenyl, pyrid-2-yl or 2-(3-{[isopropyl(methyl)amino]-methyl}phenyl).

Particularly suitable groups A^1 include those groups of the formula:



wherein m + t is 0, 1, 2, 3 or 4, preferably 1 or 2, the dotted line represents an optional bond and J is CH_2, O, S, SO, SO_2 or NH which group of the above formula may optionally be substituted by one or two methyl groups.

Favoured groups A^1 include cycloalkyl and cycloalkenyl groups of 5 or 6 ring members.

A preferred group A^1 is the cyclohexyl group.

Particularly apt compounds of this invention include those wherein one of R^1 and R^2 is a carboxy or $-Y-CO_2H$ group wherein Y is CH_2, CH_2CH_2 or CH=CH group, or a pharmaceutically acceptable salt thereof.

A preferred group R^1 is the CO_2H group or a pharmaceutically acceptable salt thereof.

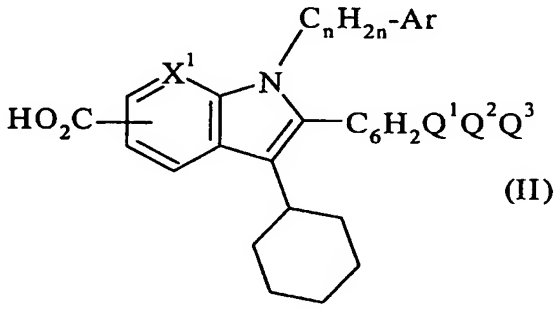
Favourably one of R^1 and R^2 is a hydrogen atom.

A favoured value for X_1 is CH.

A favoured value for X_4 is CH.

Favoured values for A^1 include non-aromatic rings. Such rings are aptly of 5 or 6 carbon atoms and which are saturated or monounsaturated. Preferred groups A^1 include cyclopentyl, cyclohexyl and cyclohexenyl groups.

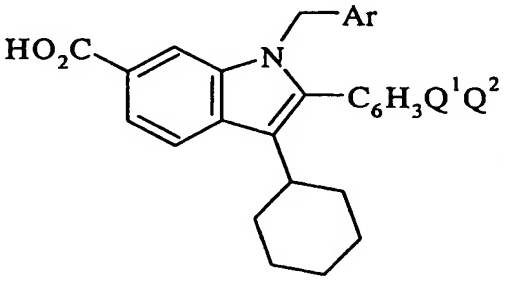
Certain particularly suitable compounds of the invention are represented by the formula (II):



(II)

wherein n, X^1, Ar, Q^1, Q^2 and Q^3 are as defined in relation to formula (I) or a pharmaceutically acceptable salt thereof.

In compounds of formulae (I) and (II) a favoured value for Q^3 is H, a favoured value for n is 1 and a favoured value for X^1 is CH so that particularly apt compounds of the invention include those of formula (III):



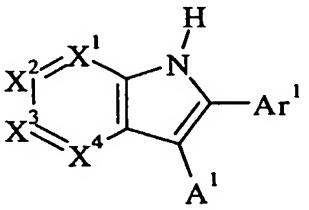
(III)

wherein Ar, Q^1 and Q^2 are defined in relation to formula (I), or a pharmaceutically acceptable salt thereof.

In certain apt compounds of formulae (II) and (III) Q^2 is hydrogen, fluorine chlorine, methyl, hydroxy, methoxy or trifluoromethyl. In certain apt compounds of formulae (II) and (III) Q^1 is hydrogen or fluorine. In certain preferred compounds of formulae (II) and (III) Q^1 is hydrogen and Q^2 is hydrogen, fluorine, methoxy or hydroxy.

The compounds of the formula (I) may be in the form of a pharmaceutically acceptable salt such as a sodium, potassium, calcium, magnesium or ammonium salt or a salt with a pharmaceutically acceptable organic base. If the compounds of the formula (I) also contain a group, the compound may be zwitterionic or in the form of a salt with a pharmaceutically acceptable acid such as hydrochloric, sulphuric, phosphoric, methane sulfonic and the like acid.

The present invention provides a process for the preparation of compounds of formula (I) and their salts which comprises the reaction of compounds of the formulae (IV) and (V):



(IV)

$$L\text{-}C_nH_{2n}\text{-}(SO_2)_p(CO)_qAr$$

(V)

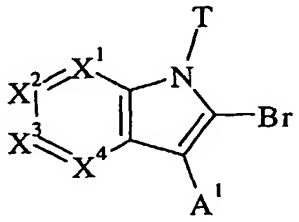
wherein X^1, X^2, X^3, X^4, A^1, Ar^1, Ar, n, p and q are as defined in relation to formula I and L is a good leaving group such as chlorine, bromine, iodine, methanesulfonate, tolyenesulfonate, triflate or the like.

In the compounds of formulae (IV) and (V) any reactions group that requires masking during the amidation reaction may be protected in conventional manner and the protecting group removed thereafter.

This principle of utilising protecting groups also applies to all other reactions described hereinafter. For example, if the desired compound of the formula I contains a CO_2H group, then the compound of the formula (IV) may contain a CO_2CH_3 group and the resulting compound of the formula (I) may be hydrolysed in conventional manner, for example with sodium hydroxide in aqueous methanol or BBr_3 in DCM to yield the compound containing the carboxylate or its sodium salt. Similarly the

substituents on the core bicycle may be elaborated after the amidation reaction, for example if the desired compound of formula (I) contains a tetrazole group then the compound of formula (IV) may contain CN group and the resulting compound of formula (I) may be reacted with an azide.

In an alternative process the compounds of formula (I) may be prepared from the corresponding compound of the formula (VI):

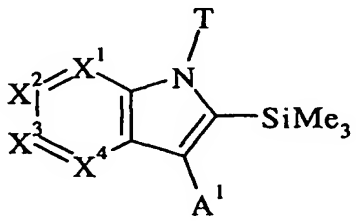


(VI)

wherein X^1, X^2, X^3, X^4 and A^1 are as defined in relation to formula (I) and T is a $C_nH_{2n}(SO_2)_p(CO)_qAr$ group by reaction with $Ar^1B(OH)_2$ in the presence of a Pd[0] catalyst under conditions conventional for the Suzuki reaction, wherein n, p, q, Ar and Ar^1 are as defined in relation to formula (I).

The compound of formula (VI) wherein T is a $C_nH_{2n}(SO_2)_p(CO)_qAr$ group can be prepared from the compound of formula (VI) wherein T is a hydrogen atom by reaction with a compound of formula (V).

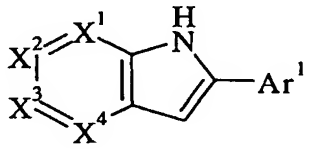
Alternatively the compound of formula (VI) may be prepared by the reaction of NBS and the compound of the formula (VII):



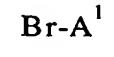
(VII)

wherein T is $C_nH_{2n}(SO_2)_p(CO)_qAr$ which may itself be prepared from the corresponding compound of formula (VII) wherein T is H by reaction with a compound of formula (V) under conventional alkylation conditions.

In an alternative synthesis the compounds of the formula (IV) may be prepared from the reaction of corresponding compounds of the formulae (VIII) and (IX):

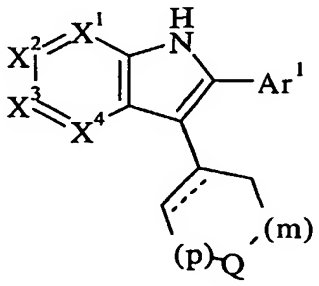


(VIII)

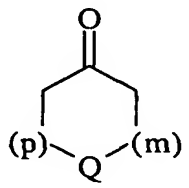


(IX)

Similarly certain compounds of the formula (X) may be prepared by the reaction of a compound of the formula (VIII) with compounds of the formula (XI):



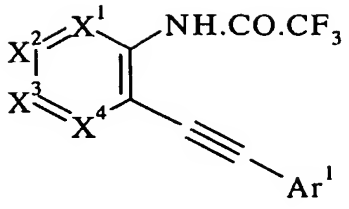
(X)



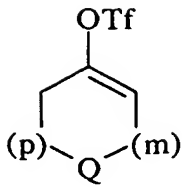
(XI)

wherein Q is CH_2, NH, O, S, SO or SO_2 and m + p is 1 or 2 and where one or two optional substituents are selected from C_{1-6} alkyl and hydroxyl and the dotted line is an optional bond; optionally followed by reduction of said optional bond.

The compounds of formula (X) may also be prepared by the reaction of the compounds of the formulae (XII) and (XIII):



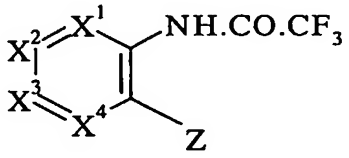
(XII)



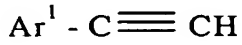
(XIII)

wherein Q, m and p are as defined in relation to formula (XI) in the presence of a Pd[0] catalyst optionally followed by reduction of the optional double bond.

The compound of the formula (XII) may be prepared from the compounds of the formulae (XIV) and (XV):



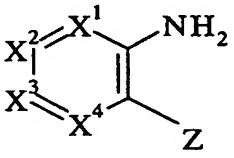
(XIV)



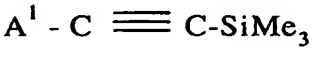
(XV)

wherein Z is I, Br or OTf in the presence of a Pd[0] catalyst.

A further process for the preparation of the compounds of formula (VII) wherein T is hydrogen comprises the reaction of the compounds of the formulae:



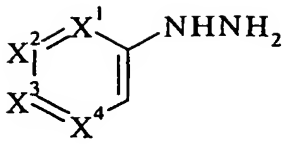
(XVI)



(XVII)

wherein Z is I, Br or OTf.

In addition, compounds of the formula (IV) may be prepared by the reaction of a hydrazine of the formula (XVIII):



(XVIII)

Ar^1-CO-CH_2-A^1

(XIX)

and a ketone of the formula (XIX).

This invention also provides compounds *per se* of formula (I) (II) or (III) except where Ar is phenyl and X^2 is an acidic function or salts and esters thereof.

The compounds of formulae (I)-(III) may be used for the inhibition of HCV polymerase and so may be used for the manufacture of medicaments which may be used to treat HCV infection.

Accordingly this invention provides a pharmaceutical composition comprising a compound of the formula (I) as hereinbefore described as a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to

about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of infection due to hepatitis C, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day. Most suitably the administration is orally using a unit done as previously indicated.

In a further aspect this invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of infection by hepatitis C virus. Most suitably the medicament is in unit dose form adapted for oral administration as indicated hereinbefore.

In another aspect this invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the treatment of infection by hepatitis C virus in a mammal and preferably in a human. Most suitably the treatment is effected by oral administration of a unit dose form as indicated hereinbefore.

The following Examples are illustrative of this invention.

The compounds of the invention were tested for inhibitory activity against the HCV RNA dependent RNA polymerase (NS5B) in an enzyme inhibition assay (example i)) and an cell based sub-genomic replication assay (described in example

ii)). The compounds generally have IC50's below 0.5 μM in the enzyme assay and EC50's typically below 20 μM in the cell based assay.

i) In-vitro HCV NS5B Enzyme Inhibition Assay

WO 96/37619 describes the production of recombinant HCV RdRp from insect cells infected with recombinant baculovirus encoding the enzyme. The purified enzyme was shown to possess in vitro RNA polymerase activity using RNA as template. The reference describes a polymerisation assay using poly(A) and oligo(U) as a primer or an heteropolymeric template. Incorporation of tritiated UTP or NTPs is quantified by measuring acid-insoluble radioactivity. The present inventors have employed this assay to screen the various compounds described above as inhibitors of HCV RdRp.

Incorporation of radioactive UMP was measured as follows. The standard reaction (50 μl) was carried out in a buffer containing 20 mM tris/HCl pH 7.5, 5 mM $MgCl_2$, 1 mM DTT, 50 mM NaCl, 0.03 % N-octylglucoside, 1 μCi [^{3}H]-UTP (40 Ci/mmol, NEN), 10 μM UTP and 10 μg/ml poly(A) or 5μM NTPs and 5μg/ml heteropolymeric template. Oligo$(U)_{12}$ (1 μg/ml, Genset) was added as a primer in the assay working on Poly(A) template. The final NS5B enzyme concentration was 5 nM. The order of assembly was: 1) compound, 2) enzyme, 3) template/primer, 4) NTP. After 1 h incubation at 22 °C the reaction was stopped by adding 50 μl of 20 % TCA and applying samples to DE81 filters. The filters were washed thoroughly with 5 % TCA containing 1M Na_2HPO_4/NaH_2PO_4, pH 7.0, rinsed with water and then ethanol, air dried, and the filter-bound radioactivity was measured in the scintillation counter. Carrying out this reaction in the presence of various concentrations of each compound set out above allowed determination of IC_{50} values by utilising the formula:

$$\% \text{ Residual activity} = 100/(1+[I]/IC_{50})^S$$

where [I] is the inhibitor concentration and "s" is the slope of the inhibition curve.

ii) Cell based HCV Replication Assay

Cell clones that stably maintain subgenomic HCV replicon were obtained by transfecting Huh-7 cells with an RNA replicon identical to I_{377}neo/NS3-3'/wt

described by Lohmann *et al.* (1999) (EMBL-genbank No. AJ242652), followed by selection with neomycin sulfate (G418). Viral replication was monitored by measuring the expression of the NS3 protein by an ELISA assay performed directly on cells grown in 96 wells microtiter plates (Cell-ELISA) using the anti-NS3 monoclonal antibody 10E5/24 (we have first described the assay in our replicon patent *WO 0259321 A2).* Cells were seeded into 96 well plates at a density of 10^4 cells per well in a final volume of 0.1 ml of DMEM/10 % FCS. Two hours after plating, 50 µl of DMEM/10 % FCS containing a 3x concentration of inhibitor were added, cells were incubated for 96 hours and then fixed for 10' with ice-cold isopropanol. Each condition was tested in duplicate and average absorbance values were used for calculations. The cells were washed twice with PBS, blocked with 5 % non-fat dry milk in PBS + 0.1 % Triton X100 + 0.02 % SDS (PBSTS) and then incubated o/n at 4^0 C with the 10E5/24 mab diluted in Milk/PBSTS. After washing 5 times with PBSTS, the cells were incubated for 3 hours at room temperature with Fc specific anti-mouse IgG conjugated to alkaline phosphatase (Sigma), diluted in Milk/PBSTS. After washing again as above, the reaction was developed with p-Nitrophenyl phosphate disodium substrate (Sigma) and the absorbance at 405/620 nm read at intervals. For calculations, we used data sets where samples incubated without inhibitors had absorbance values comprised between 1 and 1.5. The inhibitor concentration that reduced by 50 % the expression of NS3 (IC_{50}) was calculated by fitting the data to the Hill equation,

$$\text{Fraction inhibition} = 1-(Ai-b)/(A_0-b) = [I]^n / ([I]^n + IC_{50})$$

where:

Ai = absorbance value of HBI10 cells supplemented with the indicated inhibitor concentration.

A_0 = absorbance value of HBI10 cells incubated without inhibitor.

b = absorbance value of Huh-7 cells plated at the same density in the same microtiter plates and incubated without inhibitor.

n = Hill coefficient.

General Synthetic Procedures

All solvents were obtained from commercial sources (Fluka, puriss.) and were used without further purification. With the exception of routine deprotection and

coupling steps, reactions were carried out under an atmosphere of nitrogen in oven dried (110 °C) glassware. Organic extracts were dried over sodium sulfate, and were concentrated (after filtration of the drying agent) on rotary evaporatorators operating under reduced pressure. Flash chromatography was carried out on silica gel following published procedure (W.C. Still *et al.*, J. Org. Chem. **1978**, *43*, 2923) or on commercial flash chromatography systems (Biotage corporation and Jones Flashmaster) utilising pre-packed columns.

Reagents were usually obtained directly from commercial suppliers (and used as supplied) but a limited number of compounds from in-house corporate collections were utilised. In the latter case the reagents are readily accessible using routine synthetic steps that are either reported in the scientific literature or are known to those skilled in the art.

^{1}H nmr spectra were recorded on Bruker AM series spectrometers operating at (reported) frequencies between 300 and 600 MHz and unless otherwise stated were recorded at 300K. Chemical shifts (δ) for signals corresponding to non-exchangeable protons (and exchangeable protons where visible) are recorded in parts per million (ppm) relative to tetramethylsilane and are measured using the residual solvent peak as reference. Signals are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad, and combinations thereof); coupling constant(s) in hertz; number of protons. Mass spectral (MS) data were obtained on a Perkin Elmer API 100 operating in negative (ES^-) or positive (ES^+) ionization mode and results are reported as the ratio of mass over charge (*m/z*) for the parent ion only. Preparative scale HPLC separations were carried out on a Waters Delta Prep 4000 separation module, equipped with a Waters 486 absorption detector or on a Thermoquest P4000 equipped with a UV1000 absorption detector. In all cases compounds were eluted with linear gradients of water and acetonitrile both containing 0.1% TFA using flow rates between 15 and 25 mL/min.

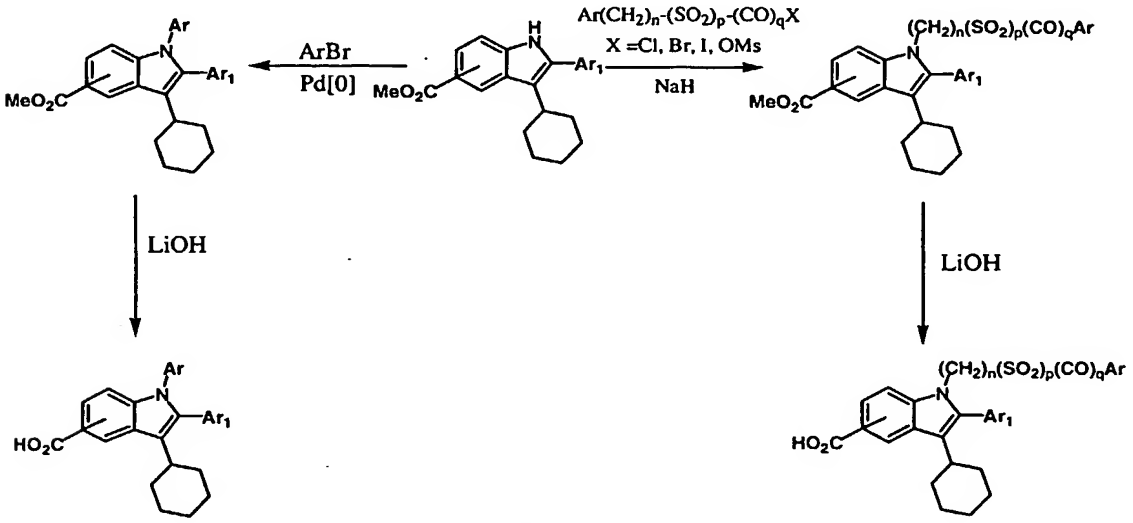
The following abbreviations are used in the examples, the schemes and the tables:

DMF: dimethylformamide; DMSO: dimethylsulfoxide; eq.: equivalent(s); AcOEt: ethyl acetate; Et_2O: diethyl ether; MeCN: acetonitrile; h: hour(s); Me: methyl; EtOH: ethanol; min: minutes; Ph: phenyl; HPLC: reversed phase high-pressure liquid

chromatography; TFA: trifluoroacetic acid; THF: tetrahydrofuran; MeOH: methanol; TFAA: trifluoroacetic anhydride

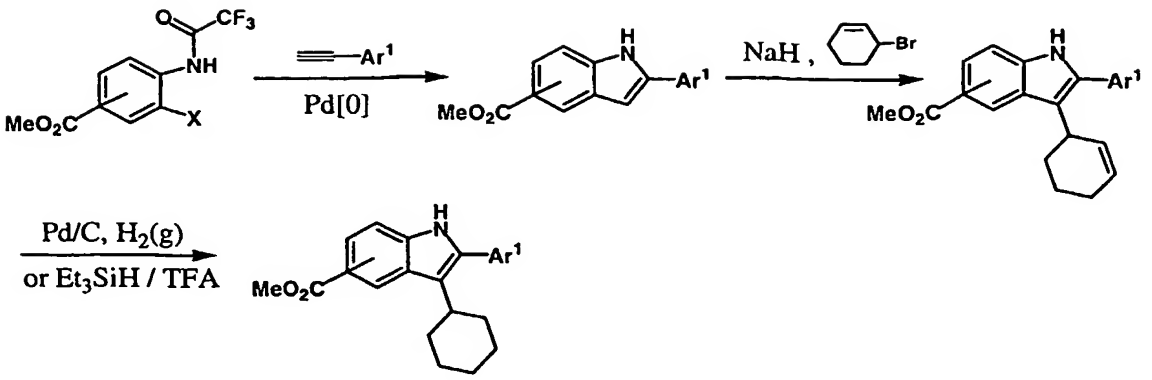
Representative Synthetic Procedures

Compounds from the invention were prepared by functionalisation of an N-unsubstituted 2-aryl-3-cycloalkyl indole carboxylic ester as outlined in *scheme* 1.



Scheme 1

Several routes are reported in the literature that may be used to access 2-aryl-3-cycloalkyl indole carboxylic ester. Useful references include: Nanomoto et al, J. Chem. Soc. Perkin I, 1990, III; Freter, J. Org. Chem., 1975, 40, 2525; Cacchi et al, Eur. J. Org. Chem., 2002, 2671; Ujjainwalla, Tetrahedron Lett., 1998, 39, 5355; Wang et al, J. Org. Chem., 2000, 65, 1889; Larock, J. Org. Chem., 1998, 63, 7652; Kelly et al, J. Org. Chem., 1996, 61, 4623; and Cacchi, Tetrahedron Lett., 1992, 33, 3915. The synthetic route used in the current work is shown in *scheme* 2.



Scheme 2

Example 1. 1-benzyl-3-cyclohexyl-2-phenyl-1*H*-indole-5-carboxylic acid

Step 1: methyl 3-iodo-4-[(trifluoroacetyl)amino]benzoate

A solution (0.26 M) of the substrate in dry THF was treated dropwise at 0 °C with TFAA (2 eq). The mixture was stirred for 10 min, then adjusted to pH 8 by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with AcOEt and the organic phase was washed with brine then dried. Removal of the solvent gave the title compound (100 %) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 3.89 (s, 3H), 7.57 (d, *J* 8.2 Hz, 1H), 8.03 (dd, *J* 1.9, 8.2 Hz, 1H), 8.44 (d, *J* 1.9 Hz, 1H)

Step 2: methyl 3-(phenylethynyl)-4-[(trifluoroacetyl)amino]benzoate

A solution (0.2 M) of methyl 3-iodo-4-[(trifluoroacetyl)amino]benzoate in a 4:1 mixture of diethylamine/DMF was treated with phenyl acetylene (1.2 eq) and $Pd(PPh_3)_2Cl_2$ (0.02 eq). The solution was stirred for 5 min. then treated with CuI (0.01 eq). After 12 h the reaction was diluted with Et_2O aqueous HCl (1 N) then the organic phase was separated and washed with brine and dried. Removal of the solvent gave a residue that was purified by flash chromatography on silica gel (9:1 AcOEt:petroleum ether) to afford the title compound (71 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.89 (s, 3H), 7.42-7.50 (m, 3H), 7.50-7.57 (m, 2H), 7.68 (d, *J* 8.4Hz, 1H), 8.04 (dd, *J* 2.0, 8.4 Hz, 1H), 8.16 (d, *J* 2.0 Hz, 1H), 11.45 (s, 1H)

Step 3: methyl 3-cyclohex-1-en-1-yl-2-phenyl-1*H*-indole-5-carboxylate

A solution (0.2 M) of methyl 3-(phenylethynyl)-4-[(trifluoroacetyl)amino]benzoate in MeCN was treated with cyclohex-1-en-1-yl trifluoromethanesulfonate (1.0 eq) and

K_2CO_3 (5.0 eq). $Pd(PPh_3)_4$ (0.05 eq) was added and the mixture was stirred at room temperature for 2 h. After dilution with Et_2O and aqueous HCl (1 N) the organic layer was separated and washed with water and brine then dried. Removal of the solvent afforded the title compound (80 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.70 (s, 4H), 2.08 (s, 2H), 2.16 (s, 2H), 3.84 (s, 3H), 5.83 (s, 1H), 7.36 (t, *J* 7.4 Hz, 1H), 7.35 (d, *J* 8.4 Hz, 1H), 7.49 (t, *J* 7.4 Hz, 2H), 7.70 (d, *J* 7.4 Hz, 2H), 7.74 (dd, *J* 1.5, 8.4Hz, 1H), 8.14 (s, 1H), 11.73 (s, 1H).

Step 4: methyl 3-cyclohexyl-2-phenyl-1*H*-indole-5-carboxylate

A solution (0.05 M) of methyl 3-cyclohex-1-en-1-yl-2-phenyl-1*H*-indole-5-carboxylate in MeOH was treated with 50 wt % Pd/C (10 % by weight) and ammonium formate (4.0 eq). The mixture was stirred under reflux for 5 h then cooled and filtered. The filtrate was treated with fresh catalyst and and ammonium formate as above and heated under reflux for 10 h. The cooled solution was filtered and concentrated to give the title compound as an oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20-1.45 (m, 3H), 1.70-1.90 (m, 5H), 1.90-2.06 (m, 2H), 2.76-3.04 (m, 1H), 3.88 (s, 3H), 7.41 (d, *J* 8.4 Hz, 1H), 7.41-7.46 (m, 1H), 7.49-7.58 (m, 4H), 7.72 (d, *J* 8.4 Hz, 1H), 8.42 (s, 1H), 11.55 (s, 1H).

Step 5: 1-benzyl-3-cyclohexyl-2-phenyl-1*H*-indole-5-carboxylic acid

A solution (0.06 M) of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-5-carboxylate in dry THF was treated with NaH (1.4 eq) then stirred at room temperature for 0.5h. Benzyl bromide (1.15 eq) was added and the mixture was stirred for 5 h. The solvent was removed, and the residue was diluted to 0.05 M with CH_2Cl_2. BBr_3 (3.0eq) was added and the mixture was stirred for 0.5 h then concentrated *in vacuo*. The residue was treated with H_20 then purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 50 % to 100 % MeCN in H_2O over 10 min) to give the title compound (16 %) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.09-1.39 (m, 3H), 1.60-1.99 (m, 7H), 2.55-2.72 (m, 1H), 5.25 (s, 2H), 6.81 (d, *J* 6.5 Hz, 2H), 7.12-7.29 (m, 3H), 7.31-7.39 (m, 2H), 7.42 (d, *J* 8.6 Hz, 1H), 7.46-7.56 (m, 3H), 7.72 (d, *J* 8.6 Hz, 1H), 8.44 (s, 1H), 12.51 (br s, 1H); MS (ES^+) *m/z* 410 $(M+H)^+$

Example 2: 1-benzyl-3-cyclohexyl-2-pyridin-2-yl-1*H*-indole-6-carboxylic acid

Step 1: methyl 3-amino-4-hydroxybenzoate

A solution (0.2 M) of acetyl chloride (3.0 eq) in MeOH was prepared at 0 °C then allowed to warm to 20 °C. 3-amino-4-hydroxybenzoic acid (1.0 eq) was added and the mixture was heated under reflux for 12 h then cooled and concentrated *in vacuo*. The residue was triturated with H_2O and dried to afford the title compound (99 %) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H), 7.15 (d, *J* 8.5 Hz, 1H), 7.79 (dd, *J* 2.1, *J* 8.5 Hz, 1H), 7.93 (d, *J* 2.1 Hz, 1H), 11.65 (br s, 1H)

Step 2: methyl 4-hydroxy-3-[(trifluoroacetyl)amino]benzoate

A solution (0.2 M) of methyl 3-amino-4-hydroxybenzoate in THF was cooled to 0 °C and treated dropwise with trifluoroacetic anhydride (2.0 eq). The mixture was stirred at 0 °C for 2 h then at 20 °C for 1 h. The pH was adjusted to 7.5 by addition of saturated aqueous $NaHCO_3$ and the solution was extracted with AcOEt. The organic layer was washed with brine and dried, then concentrated to afford the title compound (87 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (s, 3H), 7.02 (d, *J* 8.5 Hz, 1H), 7.77 (dd, *J* 2.1, *J* 8.5 Hz, 1H), 7.97 (d, *J* 2.1 Hz, 1H), 10.82 (br s, 1H)

Step 3: methyl 3-[(trifluoroacetyl)amino]-4-{[(trifluoromethyl)sulfonyl]oxy}benzoate

A solution (0.8 M) of methyl 4-hydroxy-3-[(trifluoroacetyl)amino]benzoate in dry pyridine was cooled to 0 °C and treated dropwise with trifluoromethanesulfonyl anhydride (1.15 eq). The mixture stirred for 1 h at 20 °C then diluted with H_2O and AcOEt. The organic layer was separated and washed with aqueous HCl (1 N) and brine then dried. Removal of the solvent afforded a residue that was purified by flash chromatography (1:9 AcOEt:petroleum ether eluent) to afford the title compound (64 %) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 3.92 (s, 3H), 7.82 (d, *J* 8.7 Hz, 1H), 8.11 (dd, *J* 2.2, *J* 8.7 Hz, 1H), 8.17 (d, *J* 2.2 Hz, 1H), 11.81 (s, 1H)

Step 4: methyl 2-pyridin-2-yl-1*H*-indole-6-carboxylate

A solution (0.2 M) of methyl 3-[(trifluoroacetyl)amino]-4-{[(trifluoromethyl)sulfonyl]oxy}benzoate in dry DMF was treated with 2-ethynylpyridine (2.0 eq) and tetramethylguanidine (10.0 eq). $Pd(PPh_3)_2Cl_2$ (0.1 eq)

and CuI (0.1 eq) were added and the mixture was stirred at room temperature for 0.5h. The temperature was increased to 100 °C for 8 h then the mixture was cooled and filtered through celite with Et_2O. The filtrate was washed with aqueous HCl (1 N) and brine then dried. Removal of the solvent gave a residue that was purified by flash chromatography on silica gel (15:85 AcOEt:petroleum ether) to afford the title compound as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.88 (s, 3H), 7.27 (s, 1H), 7.43-7.52 (m, 1H), 7.64 (d, *J* 8.4 Hz, 1H), 7.69 (d, *J* 8.4 Hz, 1H), 7.93 (dt, *J* 1.6, 7.7 Hz, 1H), 8.08 (d, *J* 7.7 Hz, 1H), 8.16 (s, 1H), 8.70 (d, *J* 4.9 Hz, 1H), 12.12 (s, 1H)

Step 5: methyl 3-cyclohex-2-en-1-yl-2-pyridin-2-yl-1*H*-indole-6-carboxylate

A solution (0.06 M) of methyl 2-pyridin-2-yl-1*H*-indole-6-carboxylate in DMF was cooled to 0 °C and treated with NaH (1.2 eq). The mixture was stirred at room temperature for 1 h then treated dropwise at 0 °C with a solution (0.5 M) of 3-bromocyclohexene in DMF. After stirring for 1 h in DMF the mixture was diluted with AcOEt and aqueous HCl (1 N). The organic phase was separated and washed with brine then dried. Removal of the solvent gave a residue that was purified by flash chromatography on silica gel (1:9 AcOEt:petroleum ether) to afford the title compound (18 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.62-1.81 (m, 1H), 1.83-1.98 (m, 2H), 2.00-2.33 (m, 3H), 3.88 (s, 3H), 4.28-4.48 (m, 1H), 5.75 (d, *J* 9.8 Hz, 1H), 5.86-5.96 (m, 1H), 7.42 (dd, *J* 4.8, 7.5 Hz, 1H), 7.58 (dd, *J* 1.4, 8.4 Hz, 1H), 7.76 (d, *J* 8.4 Hz, 1H), 7.80 (d, *J* 7.5 Hz, 1H), 7.99 (dt, *J* 1.7, 7.5 Hz, 1H), 8.10 (d, *J* 1.4 Hz, 1H), 8.76 (d, *J* 4.8 Hz, 1H), 11.78 (s, 1H)

Step 6: methyl 3-cyclohexyl-2-pyridin-2-yl-1*H*-indole-6-carboxylate

A solution (0.015 M) of methyl 3-cyclohex-2-en-1-yl-2-pyridin-2-yl-1*H*-indole-6-carboxylate in MeOH was treated with 20 % by weight of Pd/C (10 wt%) and stirred for 12 h under an atmosphere of hydrogen gas. The solution was purged with nitrogen then filtered. The filtrate was concentrated to afford the title compound (94 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33-1.49 (m, 3H), 1.70-1.93 (m, 5H), 1.97-2.13 (m, 2H), 3.30-3.46 (m, 1H), 3.88 (s, 3H), 7.43 (dd, *J* 4.7, 7.5 Hz, 1H), 7.60 (dd, *J* 1.5,

8.4 Hz, 1H), 7.72 (d, *J* 7.5 Hz, 1H), 7.92 (d, *J* 8.4 Hz, 1H), 7.99 (dt, *J* 1.6, 7.5 Hz, 1H), 8.10 (d, *J* 1.5 Hz, 1H), 8.77 (d, *J* 4.7 Hz, 1H), 11.69 (s, 1H)

Step 7: 1-benzyl-3-cyclohexyl-2-pyridin-2-yl-1*H*-indole-6-carboxylic acid

A solution (0.06 M) of methyl 3-cyclohexyl-2-pyridin-2-yl-1*H*-indole-6-carboxylate in dry THF was treated with NaH (1.4 eq). The mixture was stirred at room temperature for 0.5 h. Benzyl bromide (1.15 eq) was added and the mixture was stirred for 5 h. The mixture was diluted with NH_4Cl and extracted with AcOEt. The organic layer was washed with brine and dried then concentrated to give a residue that was dissolved in a 4:1 mixture of THF:H_2O (0.07 M) and treated with $LiOH.H_2O$ (4 eq). The mixture was stirred at 50 °C for 6 h then the solvent was removed. The residue was acidified with aqueous HCl (1 N) and AcOEt, and the organic layer was washed with brine and dried. The residue obtained after removal of the solvent was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 10 % MeCN to 100 % MeCN in H_2O over 12 min) to give the title compound (60 %) as a solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14-1.46 (m, 3H), 1.62-1.86 (m, 5H), 1.86-2.04 (m, 2H), 2.64-2.80 (m, 1H), 5.49 (s, 2H), 6.84 (d, *J* 6.9 Hz, 2H), 7.08-7.22 (m, 3H), 7.41-7.51 (m, 2H), 7.65 (d, *J* 8.4 Hz, 1H), 7.86-7.97 (m, 2H), 8.01 (s, 1H), 8.76 (d, *J* 4.3 Hz, 1H); MS (ES^+) *m/z* 411 $(M+H)^+$

Example 3: 1-benzyl-3-cyclohexyl-2-(4-methoxyphenyl)-1*H*-indole-6-carboxylic acid

Step 1: methyl 2-(4-methoxyphenyl)-1*H*-indole-6-carboxylate

Using the procedure described in example 2 step 4, treatment of 3-[(trifluoroacetyl)amino]-4-{[(trifluoromethyl)sulfonyl]oxy}benzoate with 4-ethynylanisole (2.0 eq) gave a residue that was purified by flash chromatography on silica gel (3:7 AcOEt:petroleum ether) to afford the title compound (51 %) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (s, 3H), 3.85 (s, 3H), 6.88 (d, *J* 1.1 Hz, 1H), 7.07 (d, *J* 8.7 Hz, 2H), 7.57 (d, *J* 8.4 Hz, 1H), 7.61 (dd, *J* 1.1, *J* 8.4Hz, 1H), 7.83 (d, *J* 8.7 Hz, 2H), 8.02 (br s, 1H), 11.79 (s, 1H)

Step 2: methyl 3-cyclohex-2-en-1-yl-2-(4-methoxyphenyl)-1H-indole-6-carboxylate

Using the procedure described in example 2 step 5, treatment of 2-(4-methoxyphenyl)-1*H*-indole-6-carboxylic acid with NaH (1.1 eq) and 3-

bromocyclohexene (1.3 eq) gave a residue that was purified by flash chromatography on silica gel (1:9 AcOEt:petroleum ether) to afford the title compound (25 %) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.55-1.75 (m, 1H), 1.85-2.02 (m, 3H), 2.05-2.30 (m, 2H), 3.65-3.77 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 5.62-5.72 (m, 1H), 5.80-5.91 (m, 1H), 7.13 (d, *J* 8.8 Hz, 2H), 7.51 (d, *J* 8.8 Hz, 2H), 7.57 (dd, *J* 8.5, 1.4 Hz, 1H), 7.64 (d, *J* 8.5 Hz, 1H), 8.00 (d, *J* 1.4 Hz, 1H), 11.49 (s, 1H)

Step 3: methyl 3-cyclohexyl-2-(4-methoxyphenyl)-1*H*-indole-6-carboxylate

Following the procedure described in example 2 step 6, treatment of 3-cyclohex-2-en-1-yl-2-(4-methoxyphenyl)-1H-indole-6-carboxylic acid with Pd/C gave the title compound (91 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15-1.45 (m, 3H), 1.65-1.85 (m, 5H), 1.85-2.10 (m, 2H), 2.75-2.95 (m, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 7.12 (d, *J* 8.7 Hz, 2H), 7.46 (d, *J* 8.7 Hz, 2H), 7.58 (dd, *J* 1.7, 8.4Hz, 1H), 7.81 (d, *J* 8.4 Hz, 1H), 7.97 (d, *J* 1.7 Hz, 1H), 11.39 (s, 1H)

Step 4: 1-benzyl-3-cyclohexyl-2-(4-methoxyphenyl)-1*H*-indole-6-carboxylic acid

A solution (0.04 M) of 3-cyclohexyl-2-(4-methoxyphenyl)-1*H*-indole-6-carboxylic acid in DMF was treated with NaH (1.5 eq) and the mixture was stirred for 1 h at room temperature. Benzylbromide (1.8 eq) was added and the mixture was stirred at room temperature for 1 h. After dilution with AcOEt the organic layer was washed with HCl (1 N) and brine then dried. Removal of the solvent gave a residue that was purified by flash chromatography on silica gel (10:90 AcOEt:PE) then diluted to 0.03 M with 1:1 THF:H_2O. LiOH.H_2O (10 eq) were added and the mixture was stirred at 40 °C for 3 days. After removal of the solvent, the residue was treated with aqueous HCl (1 N) then filtered and purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 50 % to 100 % MeCN in H_2O over 10 min; retention time: 8.0 min) to give the title compound (52 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13-1.33 (m, 3H), 1.63-1.70 (m, 1H), 1.70-1.80 (m, 4H), 1.83-1.90 (m, 2H), 2.56-2.62 (m, 1H), 3.80 (s, 3H), 5.26 (s, 2H), 6.83 (d, *J* 6.8 Hz, 2H), 7.04 (d, *J* 8.4 Hz, 2H), 7.17 (t, *J* 6.8 Hz, 1H), 7.23 (t, *J* 6.8 Hz, 2H), 7.27 (d, *J* 8.4 Hz, 2H), 7.63 (d, *J* 8.4 Hz, 2H), 7.84 (d, *J* 8.4 Hz, 2H), 7.87 (s, 1H), 12.44 (br s, 1H); m/z (ES^+) 440 $(M^+ + H)^+$.

Example 4: 3-cyclohexyl-1,2-diphenyl-1*H*-indole-6-carboxylic acid

Step 1: methyl 2-phenyl-1*H*-indole-6-carboxylate

Following the procedure described in example 2 step 4, treatment of a solution (0.3 M) of methyl 3-[(trifluoroacetyl)amino]-4-{[(trifluoromethyl)sulfonyl]oxy} with ethynyl benzene (2.0 eq), tetramethyl guanidine (10.0 eq), $PdCl_2(PPh_3)_2$ (0.1 eq) and CuI (0.1 eq) afforded a residue that was purified by flash chromatography (1:9 AcOEt:petroleum ether eluent) to afford the title compound (39 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.88 (s, 3H), 7.04 (s, 1H), 7.40 (t, *J* 7.6 Hz, 1H), 7.53 (t, *J* 7.6 Hz, 2H), 7.65 (s, 2H), 7.92 (d, *J* 7.6 Hz, 2H), 8.08 (s, 1H), 11.94 (s, 1H)

Step 2: methyl 3-cyclohex-2-en-1-yl-2-phenyl-1*H*-indole-6-carboxylate

Following the procedure described in example 2 step 5 treatment of a solution (0.06 M) of methyl 2-phenyl-1*H*-indole-6-carboxylate in dry DMF with NaH (1.1 eq) and 3-bromocyclohexene (1.3 eq) afforded a residue that was purified by flash chromatography on silica gel (1:9 AcOEt:petroleum ether) to afford the title compound (79 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.57-1.74 (m, 1H), 1.82-2.05 (m, 3H), 2.06-2.18 (m, 1H), 2.18-2.32 (m, 1H), 3.67-3.81 (m, 1H), 3.87 (s, 3H), 5.69 (d, *J* 10.4 Hz, 1H), 5.82-5.92 (m, 1H), 7.44-7.52 (m, 1H), 7.54-7.63 (m, 5H), 7.68 (d, *J* 8.4 Hz, 1H), 8.03 (s, 1H), 11.59 (s, 1H).

Step 3: methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate

A solution (0.01 M) of methyl 3-cyclohex-2-en-1-yl-2-phenyl-1*H*-indole-6-carboxylate in MeOH was treated with 10 % Pd/C (10 % wt.). The resulting suspension was stirred for 12 h under an atmosphere of hydrogen then purged with nitrogen and filtered. The filtrate was concentrated to afford the title compound (91 %) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21-1.45 (m, 3H), 1.67-1.90 (m, 5H), 1.91-2.11 (m, 2H), 2.82-2.99 (m, 1H), 3.88 (s, 3H), 7.43-7.52 (m, 1H), 7.54-7.60 (m, 4H), 7.62 (dd, *J* 1.4, 8.4 Hz, 1H), 7.87 (d, *J* 8.4 Hz, 1H), 8.02 (d, *J* 1.4 Hz, 1H), 11.51 (s, 1H).

Step 4: 3-cyclohexyl-1,2-diphenyl-1*H*-indole-6-carboxylic acid

A solution (0.05 M) of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate in toluene was treated with bromobenzene (1.2 eq) and Cs_2CO_3 (1.7 eq). $Pd(P^tBu_3)$

(0.2 eq) was added and the mixture was stirred at 100 °C for 12 h. The mixture was diluted with AcOEt then washed with brine. The dried organic phase was concentrated to give a residue that was purified by flash chromatography on silica gel (3:97 AcOEt:PE) to give a residue that was diluted to 0.03 M with a 4:1 mixture of THF:H_2O. $LiOH.H_2O$ (12 eq) was added and the mixture was stirred at 70 °C for 3 days. Following solvent removal, the residue was treated with aqueous HCl (1 N) then filtered and purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 50 % to 100 % MeCN in H_2O over 10 min; retention time: 8.9 min) to give the title compound (40 %) as a solid.

^1H NMR (400 MHz, DMSO-d_6) δ 1.19-1.40 (m, 3H), 1.66-1.70 (m, 1H), 1.77-1.81 (m, 4H), 1.91-2.07 (m, 2H), 2.67-2.78 (m, 1H), 7.22-7.25 (m, 4H), 7.29-7.36 (m, 4H), 7.41 (t, *J* 7.4 Hz, 2H), 7.70 (s, 1H), 7.71 (d, *J* 8.4 Hz, 1H), 7.94 (d, *J* 8.4 Hz, 1H), 12.55 (br s, 1H); MS (ES^-) m/z 394 $(M-H)^-$

Example 5: 1-benzyl-3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylic acid

A solution (0.05 M) of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate in THF was treated with a suspension of 60 % sodium hydride in mineral oil (1.4 eq) and the mixture was stirred for 1 h at room temperature. Following the addition of benzylbromide (1.05 eq), the mixture was stirred at 50 °C for 4 h. The solvent was removed *in vacuo* to give a residue that was diluted to 0.03 M with CH_2Cl_2. BBr_3 (3 eq) was added and the mixture was stirred for 2 h. Following solvent removal, the residue was treated with aqueous HCl (1 N) then filtered and purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 40 % to 100 % MeCN in H_2O over 11 min) to give the title compound (51 %) as a solid.

^1H NMR (400 MHz, DMSO-d_6) δ 1.15-1.36 (m, 3H), 1.63-1.69 (m, 1H), 1.70-1.81 (m, 4H), 1.83-1.92 (m, 2H), 2.54-2.63 (m, 1H), 5.30 (s, 2H), 6.81 (d, *J* 7.2 Hz, 2H), 7.15-7.24 (m, 3H), 7.34-7.35 (m, 2H), 7.46-7.50 (m, 3H), 7.65 (d, *J* 8.4 Hz, 1H), 7.86 (d, *J* 8.4 Hz, 1H), 7.91 (s, 1H), 12.49 (br s, 1H); MS (ES^+) m/z 410 $(M+H)^+$

Example 6. 3-cyclohexyl-1-(4-methylbenzyl)-2-phenyl-1*H*-indole-6-carboxylic acid

Following the procedure described in example 5, treatment of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate with NaH and 4-methylbenzyl bromide afforded a

residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 40 % to 100 % MeCN in H_2O over 11 min) to give the title compound (60 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12-1.32 (m, 3H), 1.63-1.68 (m, 1H), 1.69-1.80 (m, 4H), 1.82-1.90 (m, 2H), 2.20 (s, 3H), 2.53-2.60 (m, 1H), 5.21 (s, 2H), 6.71 (d, *J* 7.6 Hz, 2H), 7.02 (d, *J* 7.6 Hz, 2H), 7.34-7.36 (m, 2H), 7.45-7.52 (m, 3H), 7.64 (d, *J* 8.4 Hz, 1H), 7.8 (d, *J* 8.4 Hz, 1H), 7.89 (s, 1H), 12.50 (br s, 1H); MS (ES^-) m/z 422 $(M-H)^-$

Example 7. 3-cyclohexyl-1-[(2-methyl-1,3-thiazol-4-yl)methyl]-2-phenyl-1*H*-indole-6-carboxylic acid

Following the procedure described in example 5 treatment of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate with 4-(chloromethyl)-2-methyl-1,3-thiazole afforded a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 40 % to 100 % MeCN in H_2O over 11 min) to give the title compound (18 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.11-1.35 (m, 3H), 1.61-1.69 (m, 1H), 1.70-1.79 (m, 4H), 1.80-1.91 (m, 2H), 2.51-2.60 (m, 1H), 2.55 (s, 3H), 5.21 (s, 2H), 6.74 (s, 1H), 7.40-7.44 (m, 2H), 7.47-7.53 (m, 3H), 7.65 (d, *J* 8.4 Hz, 1H), 7.84 (d, *J* 8.4 Hz, 1H), 8.10 (s, 1H); MS (ES^+) m/z 431 $(M+H)^+$

Example 8. 3-cyclohexyl-1-(3-methylbenzyl)-2-phenyl-1*H*-indole-6-carboxylic acid

Following the procedure described in example 5, treatment of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate with 3-methyl benzylbromide afforded a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 40 % to 100 % MeCN in H_2O over 11 min) to give the title compound (96 %) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.19-1.36 (m, 3H), 1.65-1.92 (m, 7H), 2.19 (s, 3H), 2.52-2.66 (m, 1H), 5.24 (s, 2H), 6.55 (d, *J* 7.5 Hz, 1H), 6.70 (s, 1H), 6.99 (d, *J* 7.5 Hz, 1H), 7.10 (t, *J* 7.5 Hz, 1H), 7.35-7.38 (m, 2H), 7.49-7.55 (m, 3H), 7.66 (dd, *J* 8.4, 0.9 Hz, 1H), 7.87 (d, *J* 8.4 Hz, 1H), 7.93 (d, *J* 0.9 Hz, 1H); MS (ES^+) m/z 424 $(M+H)^+$

Example 9. 3-cyclohexyl-2-phenyl-1-(pyridin-2-ylmethyl)-1*H*-indole-6-carboxylic acid trifluoroacetate

Following the procedure described in example 5, treatment of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate with 2-(chloromethyl)pyridine hydrochloride afforded a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 10 % to 90 % MeCN in H_2O over 10 min) to give the title compound (59 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12-1.30 (m, 3H), 1.61-1.68 (m, 1H), 1.70-1.78 (m, 4H), 1.81-1.91 (m, 2H), 2.55-2.62 (m, 1H), 5.31 (s, 2H), 6.67 (d, *J* 8.0 Hz, 1H), 7.21-7.25 (m, 1H), 7.34-7.36 (m, 2H), 7.45-7.49 (m, 3H), 7.65-7.69 (m, 2H), 7.86 (d, *J* 8.4 Hz, 1H), 7.90 (s, 1H), 8.45 (d, *J* 4.8 Hz, 1H); MS (ES^+) m/z 411 $(M+H)^+$

Example 10. 3-cyclohexyl-1-[4-(methylsulfonyl)benzyl]-2-phenyl-1*H*-indole-6-carboxylic acid

Following the procedure described in example 5, treatment of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate with 1-(bromomethyl)-4-(methylsulfonyl)benzene afforded a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 40 % to 100 % MeCN in H_2O over 11 min) to give the title compound (99 %) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.18-1.37 (m, 3H), 1.66-1.98 (m, 7H), 2.55-2.69 (m, 1H), 3.15 (s, 3H), 5.42 (s, 2H), 7.05 (d, *J* 8.4 Hz, 2H), 7.34-7.38 (m, 2H), 7.47-7.52 (m, 3H), 7.69 (dd, *J* 8.4, 1.2 Hz, 1H), 7.79 (d, *J* 8.4 Hz, 2H), 7.90 (d, *J* 8.4 Hz, 1H), 7.94 (d, *J* 1.2 Hz, 1H); MS (ES^+) m/z 488 $(M+H)^+$

Example 11. 3-cyclohexyl-1-(3,5-dibromobenzyl)-2-phenyl-1*H*-indole-6-carboxylic acid

Following the procedure described in example 5, treatment of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate with 3,5-dibromobenzyl bromide afforded a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 40 % to 100 % MeCN in H_2O over 11 min) to give the title compound (68 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16-1.30 (m, 3H), 1.63-1.66 (m, 1H), 1.70-1.78 (m, 4H), 1.82-1.92 (m, 2H), 2.55-2.66 (m, 1H), 5.32 (s, 2H), 6.89 (s, 1H), 6.90 (s,

1H), 7.29-7.31 (m, 2H), 7.46-7.53 (m, 3H), 7.64 (s, 1H), 7.69 (d, *J* 8.4 Hz, 1H), 7.88 (d, *J* 8.4 Hz, 2H), 8.03 (s, 1H), 12.58 (br s, 1H); MS (ES^+) m/z 568 $(M+H)^+$

Example 12. 3-cyclohexyl-1-(1H-imidazol-4-ylmethyl)-2-phenyl-1H-indole-6-carboxylic acid trifluoroacetate

A solution (0.06 M) of (1-trityl-1H-imidazol-4-yl)methanol in CH_2Cl_2 was cooled at 0 °C. Triethylamine (5.0 eq) and methanesulfonyl chloride (2.3 eq) were added and the mixture was stirred at 0 °C for 5 h. The mixture was diluted with CH_2Cl_2 then washed sequentially with saturated aqueous $KHSO_4$ and brine. The solvent was removed *in vacuo* to afford (1-trityl-1*H*-imidazol-4-yl)methyl methanesulfonate as a solid. A solution (0.03 M) of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate in DMF was treated with NaH (1.5 eq) and stirred for 1 h at room temperature. (1-Trityl-1*H*-imidazol-4-yl)methyl methanesulfonate (2.0 eq) was added and the mixture was stirred at 80 °C for 12 h. After dilution with AcOEt the organic phase was washed with aqueous HCl (1 N) and brine. The dried organic layer was concentrated and diluted to 0.02 M with CH_2Cl_2. BBr_3 (3 eq) was added and the mixture was stirred for 2 h. Following solvent removal, the residue was treated with aqueous HCl (1 N) then filtered and purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 10 % to 90 % MeCN in H_2O over 10 min; retention time: 9.0 min) to give the title compound (54 %) as a solid.

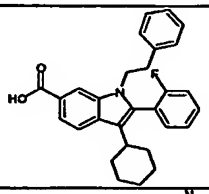
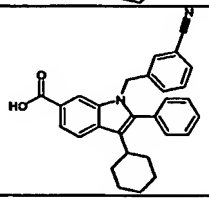
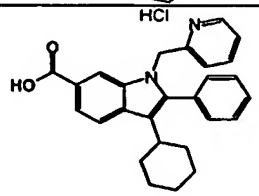
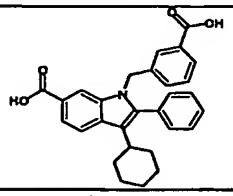
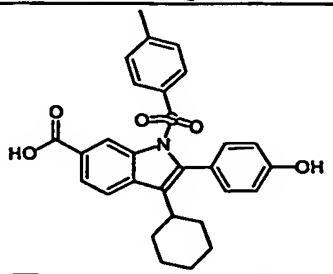
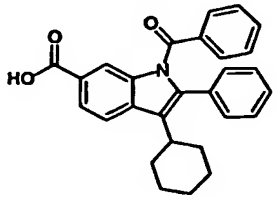
^1H NMR (400 MHz, DMSO-d_6) δ 1.17-1.31 (m, 3H), 1.65-1.74 (m, 5H), 1.81-1.90 (m, 2H), 2.53-2.60 (m, 1H), 5.32 (s, 2H), 6.93 (s, 1H), 7.36-7.42 (m, 2H), 7.49-7.56 (m, 3H), 7.71 (d, *J* 8.4 Hz, 1H), 7.89 (d, *J* 8.4 Hz, 1H), 8.07 (s, 1H), 8.85 (s, 1H); MS (ES^+) m/z 400 $(M+H)^+$

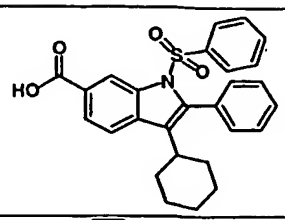
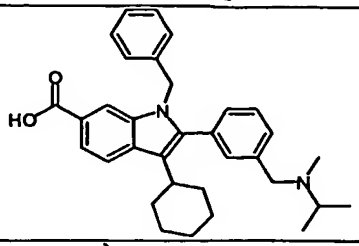
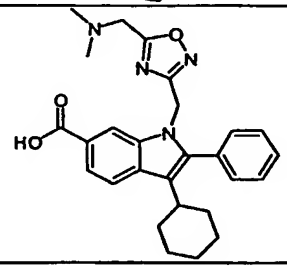
Example 13. 3-cyclohexyl-2-phenyl-1-(pyridin-3-ylmethyl)-1*H*-indole-6-carboxylic acid hydrochloride

Following the procedure described in example 5, treatment of methyl 3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylate with (3-bromomethyl)pyridine hydrobromide afforded a residue that was purified by HPLC (stationary phase: Waters Symmetry C_{18} 19x100 mm; mobile phase: 40 % to 100 % MeCN in H_2O over 11 min) to give the title compound (36 %) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12-1.31 (m, 3H), 1.63-1.68 (m, 1H), 1.70-1.78 (m, 4H), 1.81-1.92 (m, 2H), 2.53-2.62 (m, 1H), 5.44 (s, 2H), 7.32-7.35 (m, 2H), 7.43 (d, *J* 7.6 Hz, 1H), 7.47-7.51 (m, 3H), 7.52-7.56 (m, 1H), 7.69 (d, *J* 8.4 Hz, 1H), 7.89 (d, *J* 8.4 Hz, 1H), 8.04 (s, 1H), 8.20 (s, 1H), 8.55 (d, *J* 5.5 Hz, 1H); MS (ES^+) m/z 411 $(M+H)^+$

Additional Examples

Name	Structure	Molecular Ion $[M+H]^+$
3-cyclohexyl-2-(2-fluorophenyl)-1-(2-phenylethyl)-1*H*-indole-6-carboxylic acid		442
1-(3-cyanobenzyl)-3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylic acid		435
3-cyclohexyl-2-phenyl-1-(pyridin-2-ylmethyl)-1*H*-indole-6-carboxylic acid hydrochloride		411
1-(3-carboxybenzyl)-3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylic acid		454
3-cyclohexyl-2-(4-hydroxyphenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-indole-6-carboxylic acid		490
1-benzoyl-3-cyclohexyl-2-phenyl-1*H*-indole-6-carboxylic acid		424

3-cyclohexyl-2-phenyl-1-(phenylsulfonyl)-1*H*-indole-6-carboxylic acid		460
1-benzyl-3-cyclohexyl-2-(3-{[isopropyl(methyl)amino]-methyl}phenyl)-1*H*-indole-6-carboxylic acid		495
3-cyclohexyl-1-({5-[(dimethylamino)methyl]-1,2,4-oxadiazol-3-yl}methyl)-2-phenyl-1-1*H*-indole-6-carboxylic acid		459